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those other natural products which will either supply abundantly the deficiencies or act as an 'antidote' to any inherent toxicity.

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[1] Hart, E. B., McCollum, E. V., Steenbock, H., and Humphrey, G. C., *Wisconsin Exp. Sta. Research Bull.* No. **17**, 1911.

[2] Stepp, W., *Zs. Biol., München*, **57**, 1912, (135) 62, 1913, (405); Hopkins, F. G., *J. Physiol.* **44**, 425, 1912; Funk, C., *Zs. Physiol. Chem.*, **88**, 1913; (352), **92**, 1914, (13); McCollum, E. V., and Davis, M., *J. Biol. Chem.*, **15**, 1913; (167), **23**, 1915, (231); Osborne, T. B. and Mendel, L. B. *Ibid.*, **15**, 1913, (311).

[3] McCollum, E. V., and Kennedy, C., *J. Biol. Chem.*, **24**, 1916, (491).

[4] Hart, E. B., and McCollum, E. V., *Ibid.*, **19**, 1914, (373); McCollum, E. V., and Simmonds, N., and Pitz, W., *Ibid.*, **25**, 1916, (105); Hart, E. B., Miller, W. C., and McCollum, E. V., *Ibid.*, **25**, 1916, (239).

[5] Hart, E. B., Miller, W. C., and McCollum, E. V., *Ibid.*, **25**, 1916, (239); McCollum E. V., Simmonds, N., and Pitz, W., *Ibid.*, **25**, 1916, (105).

WHAT DETERMINES THE DURATION OF LIFE IN METAZOA?

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1. It can be stated as a fact that most if not all organisms have a characteristic duration of life. To give extreme examples, many insects have a duration of life measured in weeks only, while the Californian sequoia has a duration of life of thousands of years, and in the human being the duration of life is proverbially three score and ten. The question arises: What determines this characteristic duration of life?

Bütschli was the first to point out that unicellular organisms have an unlimited duration of life and this idea has become very popular through Weismann. All recent researches support the correctness of this idea. As a consequence we are forced to the conclusion that natural death is a phenomenon found almost exclusively in organisms which are composed of different organs. The idea that natural death is connected with the compound character of organisms is supported by two facts; namely, first, the observation that a cutting will survive the whole plant, while the cutting if not separated would have died with the whole plant. By the method of cuttings the life of the individual plant can be prolonged apparently indefinitely.

The second fact is that if we take pains to transplant certain cells from an old organism successively to young organisms, these cells will outlive the original individual indefinitely—they are, in other words, immortal. The proof can only be furnished with the aid of marked cells and Leo Loeb selected for this purpose the cancer cell which is easily distinguishable from other cells by its rapid growth. He thus showed that the cancer cell is apparently immortal and the same could possibly be shown for many other tissue cells if it were only possible to mark them and thus follow them individually through a series of successive graftings.

The experiments on hybridization also support the idea that natural death is due to some maladjustment in a compound organism. By fertilizing an egg with the sperm of another species we can bring about a shortening of the duration of life to an almost infinitely small fraction of the normal duration; and in some cases the opposite result may also be obtained. It depends whether in the hybrid the maladaptation of the parts is greater or smaller than in the pure breed. The problem then before the biologist is to find out the physicochemical character of this maladaptation which results in old age and death.

2. In certain organisms life is divided into two or more well defined morphological periods separated by an equally well defined process, the metamorphosis. Thus in the frog the metamorphosis from the tadpole stage consists in the growth of the legs and the absorption of the tail and gills. We know now through Gudernatsch that this metamorphosis can be brought about at any time by feeding the tadpole with thyroid, and it is possible that the natural duration of the tadpole stage is determined by the production of a certain quantity of a substance, possibly a specific constituent or product of the thyroid gland in the tadpole. This substance acts on many different organs in the body in a different way, causing the buds of the legs to grow and causing the tail and the gills to die by autolysis and by phagocytosis.

This suggests the possibility that the termination of the second stage in the frog's life, namely natural death, is also determined by the production in the body of one (or more) substances which bring about the termination of the second stage of life as definitely as the thyroid substance terminates the tadpole stage. It matters little whether we call such substances terminating one of the stages in life hormones or poisons.

3. In order to test the validity of such reasoning we have approached the problem by a method which one of us suggested in 1908[1] for this purpose, namely by ascertaining whether there is a temperature coefficient for the duration of life.

It is definitely established that a number of life phenomena have a temperature coefficient characteristic of chemical reactions, namely of about 2 for a difference of temperature of about 10°C.; although at the lower and upper temperature limit this coefficient changes more rapidly than it is usually found to change in purely chemical processes. This might be interpreted to mean that the order of magnitude of the rate of such life phenomena and of chemical reactions is the same and that such life phenomena are due to definite chemical reactions, e.g., a reaction resulting in the formation of a hormone. Such a temperature coefficient was first observed by F. Lillie and Knowlton for the development of the egg of the frog and has since been found to exist generally.

If we could show that in a species with a definite metamorphosis there exists not only a definite temperature coefficient for the duration of life of the order of that of a chemical reaction, but that this coefficient is approximately identical with the temperature coefficient of the duration of the larval stage or stages, we should not have certainty but at least some probability that the duration of life is determined by causes similar to those which determine the duration of the larval stages. Our experiments were made on the fruit fly which has three definite stages, larval, pupa, and imago. We have already reported on some experiments in this direction[2] but our new experiments were made on forms which had been freed from all microorganisms. This was necessary on account of Metchnikoff's suggestion that poisons formed by intestinal microorganisms play an important rôle in limiting the duration of life.

Moreover, in our previous experiments only water or sugar solutions were offered to the flies and it was necessary to keep them on adequate food. It was found that on 2% glucose-agar the flies lived as long as on their natural food, yeast or yeast-agar. We preferred glucose-agar since it does not allow the larvae to hatch and we had to guard against this possibility since otherwise it would have been impossible to obtain correct figures for the death rate of the old flies. About 20 flies were kept in a large flask and about 8 to 10 different flasks with flies were used for the determination of life for any one temperature. The number of flies which died were counted each day and the duration of life for each temperature is the average for all the cultures kept at this temperature. The experiments were carried on in thermostats whose temperature was constant within one-tenth of a degree. The temperatures selected were 30°, 25°, 20°, 15°, and 10°. Table 1 gives the duration of the three stages for the different temperatures with the probable error.

These figures show, first, that the temperature coefficient for the larval stage, the pupa stage, and the life of the imago is of the order of 2 or above for 10°C., which is characteristic for both chemical reactions and life phenomena in general.

They show in addition, however, that the ratio of the duration of the three stages is approximately constant for all temperatures as far as our experiments go. The ratios are given in table 2.

The values for the ratios at 15°, 20°, and 25° agree very well, while at 30° the value for the imago falls off; one of the cultures at 30° gave, however, the value of 0.22.

We may, therefore, say that as far as our present experiments go the ratio of the duration of life of the insect to the duration of the larval stage is approximately constant for all temperatures and that the same is true for the ratio of the larval to the pupa stage.

If it is permissible to consider the production of a hormone as the limiting factor for the duration of the larval stage we face the possibility that the production of a hormone (or a poison) may be also the limiting factor for the duration of the imago stage and the duration of a normal life in general.

TABLE 1

DURATION OF THE THREE STAGES OF THE LIFE OF *Drosophila* IN DAYS

STAGES	10°	15°	20°	25°	30°	31.5°
Larva....	56.8 ±1.1	18.0 ±0.2	8.38 ±0.04	6.32 ±0.04	4.62 ±0.04	4.9 ±0.05
Pupa....	Does not hatch	13.5 ±0.2	6.1 ±0.1	4.22 ±0.03	3.43 ±0.04	
Imago[3]...			40.0 ±0.9	28.5 ±0.2	13.7 ±0.4	
Total length of life................			54.5	39.0	21.7	

TABLE 2

RATIO OF DURATION OF THE THREE STAGES

STAGES	15°	20°	25°	30°
Larva: pupa....................	1.31 ±0.03	1.37 ±0.03	1.49 ±0.02	1.35 ±0.02
Larva: imago..................		0.21 ±0.2	0.22 ±0.1	0.33 ±0.1

On the basis of this assumption we can readily understand that by inadequate feeding of the larva the duration of the larval stage may be prolonged since the inadequate feeding may delay the formation of the hormone responsible for metamorphosis. It would be wrong to state that the duration of the larval stage is determined by the energy value of the food taken up by a normal larva since in the frog at least the larval period can apparently be prolonged indefinitely if certain hormones are lacking though the larva may grow considerably during this period. In the experiments on parthenogenetic frogs one of us has twice obtained a tadpole unable to metamorphose in a year or in a year and a half. One of these had grown beyond the normal tadpole size. The latter was finally fed thyroid and began to metamorphose within a week. Both tadpoles were almost albinotic and from a recent paper by Allen it seems possible that in both larvae the hypophysis was abnormally developed or lacking. It is obvious that the production of a definite hormone and not the calory value of food is the limiting factor for the duration of the larval period.

4. *Conclusion.*—The experiments show that *Drosophila* has a temperature coefficient for the duration of life of the order of magnitude of that of a chemical reaction. Since the animals used in our experiments were absolutely free from microorganisms this influence of temperature on the duration of life cannot be attributed to bacterial poisons.

It was found, moreover, that the duration of the pupa stage is at each temperature proportional to the duration of the larval stage and that the same proportionality exists between the duration of the life of the insect to the larval stage, as far as our present experiments go. Since we know that the duration of the larval stage is determined by a specific hormone we are compelled to consider the possibility that the duration of life is also primarily determined by the formation of poisonous substances or a hormone in the body.

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[1] Loeb, J., *Arch. ges. Physiol., Bonn,* 124, 1908, (411); Moore, A. R., *Arch. Entw.-Mech., Leipzig,* 29, 1910, (287). For a fuller discussion of the subject see Loeb, *The Organism as a Whole,* New York, 1916.

[2] Loeb, J., and Northrop, J. H., these PROCEEDINGS, 2, 1916, (456).

[3] The experiments on the duration of life of the imago at 10° and 15° are not yet completed. From present indications it seems that for 15° the duration of life is in the neighborhood of ninety days, which agrees with the value expected according to the theory. At 10° the flies have been alive for ninety days and have not yet begun to die.

THE INTERRELATION BETWEEN DIET AND BODY CONDITION AND THE ENERGY PRODUCTION DURING MECHANICAL WORK IN THE DOG

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A dog weighing 8 kgm., in poor nutritive condition, was received into the laboratory. His basal metabolism, as measured during a period of absolute rest eighteen hours after partaking of an adequate standard diet, was 17.6 calories per hour. Traveling at the rate of 2.5 miles (4.0 km.) per hour he required 11.0 calories above the basal to move his body 1000 meters during the period beginning about eighteen hours after food ingestion, whereas 11.2 calories were required if 70 grams of